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PHYSIOLOGICAL REVIEW

The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnoea

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SUMMARY

Intermittent hypoxia and unstable breathing are key features of obstructive sleep apnoea (OSA), the most common pathological problem of breathing in sleep. Unstable ventilatory control is characterised by high loop gain (LG), and likely contributes to cyclical airway obstruction by promoting airway collapse during periods of low ventilatory drive. Potential new strategies to treat OSA include manipulations designed to lower LG. However, the contribution of inherent versus induced LG abnormalities in OSA remains unclear. Hence, a better understanding of the mechanisms causing high LG in OSA is needed to guide the design of LG based treatments. OSA patients exhibit abnormal chemoreflex control which contributes to increased LG. These abnormalities have been shown to normalise after continuous positive airway pressure treatment, suggesting induced rather than inherent trait abnormalities. Experimental intermittent hypoxia, mimicking OSA, increases hypoxic chemosensitivity and induces long term facilitation; a sustained increase in ventilatory neural output which outlasts the original stimulus. These neuroplastic changes induce the same abnormalities in chemoreflex control as seen in OSA patients. This review outlines the evidence to support that a key component of high LG in OSA is induced by intermittent hypoxia, and is reversed by simply preventing this inducing stimulus.

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Introduction

Obstructive sleep apnoea (OSA) is characterised by repeated partial (hypopnoea) or complete (apnoea) collapse of the airway during sleep resulting in bouts of combined hypercapnia and hypoxia. OSA is the most common sleep disorder and is estimated to affect between 10% of men and 3% of women aged 30–49 y, and 17% of men and 9% of women aged 50–70 y [1]. OSA is associated with increased mortality and morbidities including cardiovascular disease [2], diabetes [3], cognitive impairment [4], pathological daytime sleepiness [5] and increased frequency of driving and other accidents [6]. Continuous positive airway pressure (CPAP) is the main treatment for OSA, however long term adherence is poor, with ≤50% of patients accepting and tolerating CPAP long term [7]. Consequently there is a strong ongoing need for the development of alternative treatments. OSA pathophysiology is now understood to involve multiple interacting factors including increased airway collapsibility (typically measured from airway critical closing pressure), a propensity to wake to airway obstruction (low arousal threshold), poor upper airway muscle recruitment responses and unstable ventilatory control (high loop gain, LG), with variable combinations producing differing OSA phenotypes between individuals [8]. Wellman and colleagues have recently proposed new diagnostic methods designed to quantify these causal factors in each patient, thus allowing treatments to be tailored to each individual [8]. High LG has been reported in 36% of CPAP treated patients [9], and could play a significant pathogenic role in a greater proportion of previously untreated OSA patients. Given the prevalence of LG disturbances, a key part of this individualised treatment approach could include pharmacological or non-pharmacological manipulation of LG [10]. However it remains unclear if high LG is an inherent causal trait in OSA and/or an induced effect exacerbating OSA and contributing to disease progression. A greater understanding of the inherent versus induced mechanisms underpinning high LG in OSA is therefore needed to effectively guide treatments designed to reduce LG.

LG includes “plant” (respiratory apparatus) and “controller” (chemoreflex) gain components, both of which can be abnormal in OSA. Increased plant gain may predominantly reflect obesity effects

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Abbreviations

AIH	acute intermittent hypoxia
AHI	apnoea hypopnoea index
CIH	chronic intermittent hypoxia
CPAP	continuous positive airway pressure
HCVR	hypercapnic ventilatory response
hLTF	hypoglossal long term facilitation
HVR	hypoxic ventilatory response
IH	intermittent hypoxia
LTF	long term facilitation
LG	loop gain
OSA	obstructive sleep apnoea
$PaCO_2$	arterial CO_2 partial pressure
PaO_2	arterial O_2 partial pressure
$P_{ET}CO_2$	end tidal partial pressure of CO_2
pLTF	phrenic long term facilitation
PA	progressive augmentation
ROS	reactive oxygen species
sLTF	sensory long term facilitation
$_{UA}$LTF	upper airway long term facilitation
V_I	minute ventilation
V_T	tidal volume
$_V$LTF	ventilatory long term facilitation

on lung volume that may normalise while using CPAP [11]. However, OSA patients also exhibit abnormally elevated controller gain independent of BMI [12–14]. These chemoreflex control abnormalities have been shown to normalise following ≥1 mo of CPAP use [13,15,16], supporting that high controller gain is predominantly induced rather than an intrinsic trait in OSA.

Several stimuli experienced during obstructed breathing events have been shown to induce lasting changes in ventilatory neural responses. Intermittent hypoxia (IH) induces neuroplastic changes in the carotid bodies [17], brainstem [18], and cervical spinal cord [19], inducing increased hypoxic sensitivity [17] and long term facilitation (LTF) of various ventilatory nerves, manifesting as a sustained increase in neural output to a given stimulus [20]. LTF of ventilatory neural output has been studied and demonstrated in a variety of species including humans [21], dogs [22], cats [23], goats [24], rats [25] and avian species such as ducks [26]. LTF is thus highly conserved across phylogenetically distant species suggesting an important adaptive mechanism in ventilatory neural control. However, as with many physiological processes in disease states, LTF could play both adaptive and maladaptive roles in OSA pathophysiology and both have been posited [27,28]. On the one hand hypoglossal LTF may augment upper airway dilator muscle activity to help prevent airway collapse [27]. However, experimental IH also induces the same abnormalities in chemoreflex control that are seen in OSA patients [21,29,30], which increase controller and therefore overall LG, suggesting IH induced neuroplasticity may worsen OSA. These neuroplastic changes appear to gradually decay following return to room air breathing for several days [17,31–33], much the same as chemoreflex abnormalities in OSA normalise with CPAP use [13,15,16]. These data support that normalisation of LG may simply require prevention of IH and allowing sufficient time for chemoreflex control, and therefore controller gain, to readjust. Although lowering LG may not cure OSA given other contributory factors, IH induced high LG likely exacerbates OSA in a feed-forward manner. Neuroplasticity effects on LG have several treatment implications; including lowered pressures over time that could improve long-term CPAP adherence, the development of drug therapies targeting the cellular mechanisms contributing to raised LG, and future combination treatments where LG lowering may be achieved with short term conventional treatments such as CPAP by simply preventing the inducing IH stimulus.

This review summarises the evidence to support a pathogenic role for abnormal chemoreflex control and high LG in OSA, and further evidence to support that these effects are predominantly induced by OSA and reverse with treatment. The main focus is on animal and human studies supporting that IH induced neuroplasticity is the main causal mechanism inducing high controller gain and therefore overall LG in OSA. Implications for treatment and future research are also discussed.

Sleep chemoreflex control

Resting end-tidal CO_2 (end tidal partial pressure of CO_2 ($P_{ET}CO_2$), an indirect estimate of arterial CO_2 partial pressure ($PaCO_2$)) determines the position of eupnoea on the so called metabolic hyperbola, which governs the relationship between changes in CO_2 when ventilation changes at a given rate of metabolic CO_2 production. During sleep, ventilation below eupnoea decreases linearly with reducing $P_{ET}CO_2$ until an "apnoeic threshold" 3–6 mmHg below eupnoea is reached, where ventilation is totally suppressed [34]. Above eupnoea, ventilation increases linearly with $P_{ET}CO_2$ and the slope of this relationship indicates CO_2 chemoreflex sensitivity. Following hypocapnic central apnoea during sleep or anaesthesia (e.g., after withdrawal of mechanical hyperventilation to induce central apnoea), $PaCO_2$ must rise several mmHg above not only the level of CO_2 which induced apnoea, but also to a level above the resting eupnoeic level called the ventilatory recruitment threshold, before rhythmic breathing is reinitiated [35,36]. This contrasts with wakefulness, where hypocapnia does not induce central apnoea, and ventilation is maintained at a stable baseline level below a CO_2 chemoreflex threshold [37], above which ventilation rises linearly with increasing $P_{ET}CO_2$ [38].

During hypoxaemia mammals exhibit a characteristic biphasic hypoxic ventilatory response (HVR). Initially, there is an acute HVR during which ventilation increases with decreasing arterial O_2 (PaO_2). If hypoxia is sustained the acute response is followed by a decrease in ventilation called hypoxic ventilatory decline [39]. The HVR modulates ventilation via the combined effects of O_2 and CO_2 on peripheral chemoreflex responses [38,40], with hypoxia increasing the sensitivity to CO_2 unless $PaCO_2$ is below the chemoreflex threshold, below which the HVR is suppressed [41]. Increased minute ventilation (V_I) during hypoxia results in a reduction of $P_{ET}CO_2$ which tends to constrain the HVR. During sleep, hypoxia does not alter the apnoeic threshold, therefore the point of eupnoea moves closer to the apnoeic threshold, reducing the CO_2 reserve and increasing the slope of the ventilatory response to CO_2 below eupnoea [42].

Ventilatory control stability – loop gain

Loop gain is an engineering concept usefully applied in many negative feedback control systems, such as the chemoreflex control of breathing, to quantify the overall stability of the feedback control system. LG is the ratio of a control systems response relative to the magnitude of the disturbance eliciting the response, and incorporates three main components; controller gain, plant gain and the feedback delay between the controller and plant. In ventilatory control, controller gain reflects chemoreflex sensitivity ($\Delta V/\Delta PaCO_2$ and/or ΔPaO_2), plant gain reflects the magnitude of change in blood

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gases per unit change in ventilation ($\Delta PaCO_2$ and/or $\Delta PaO_2/\Delta V$), and the delay gain is determined by circulatory delay and mixing of gases between the blood and tissue compartments [43]. If the response to a ventilatory disturbance is smaller than the initial disturbance, LG is less than unity and ventilatory perturbations following a disturbance dampen over time. However, if LG is equal to unity or greater, disturbances become self-perpetuating and amplified respectively and respiratory control is inherently unstable (See [44] for a review).

LG can be mathematically quantified by fitting measures of ventilation and blood gas disturbances to feedback models of ventilatory control to estimate gain parameters of the model. Measures obtained by traditional chemoreflex tests also provide some insight into controller, plant and overall LG. Chemoreflex effects on ventilatory control stability during sleep have been reviewed elsewhere [35,43] and therefore will only be discussed briefly.

LG is not a constant and changes dynamically in any non-steady state, such as over the course of obstructed breathing. This reflects a range of factors such as changing blood gases, lung volume, negative intra-thoracic pressures, upper airway dilator muscle activity and airway resistance, which can all influence the dynamics of chemoreflex responses [45]. Traditional chemoreflex breathing tests measure only the gain component of overall LG under near steady-state conditions. These measures are nevertheless useful to consider in the context of respiratory control stability and overall LG.

When considering ventilatory control in the context of OSA the most important factors are CO_2 at eupnoea, chemoreflex sensitivity above eupnoea, the CO_2 apnoeic threshold and the modulatory effects of hypoxia on the CO_2 response curve. The position of eupnoea is most relevant as the slope above and below eupnoea during sleep or anaesthesia may not be the same [35], and even though central apnoea is not characteristic of OSA, the apnoeic threshold will determine the slope of the ventilatory response below eupnoea.

An elevated chemoreflex gain component of overall LG increases the magnitude of hyperventilation and hypocapnia after recovery from obstruction, and this could promote subsequent airway collapse through reduced upper airway dilator muscle activity that helps defend the airway from collapse (see [35,43] for review). Elevated LG may occur due to increased sensitivity (controller gain i.e., slope of the chemoreflex response curve) to either hypercapnia or hypoxia (above eupnoea) without any change in the position of eupnoea or the apnoeic threshold (Fig. 1A). However, changes in the apnoeic threshold and/or eupnoea can also narrow the CO_2 difference from these inflection points, and increase the sensitivity (controller gain) to CO_2 below eupnoea (Fig. 1B), potentially exacerbating the reduction in upper airway muscle activity for any degree of hypocapnia. A leftward shift in the position of eupnoea without any change in controller gain above eupnoea would still increase the ventilatory response for any given level of CO_2 above eupnoea (Fig. 1C1) to promote greater hyperventilation. However, if there was no change in controller gain below eupnoea (i.e., a concomitant leftward shift in the apnoeic threshold), the CO_2 reserve between eupnoea and the apnoeic threshold would increase due to the left-ward steepening slope of the metabolic hyperbola (Fig. 1C2). This effect could potentially help protect against respiratory instability. In addition, as eupnoea shifts leftward along the metabolic hyperbola plant gain is reduced (due to the changing slope of the metabolic hyperbola), such that a greater ventilatory increase would be required to achieve the same reduction in $PaCO_2$ (Fig. 1D). Consequently, a leftward shift along the metabolic hyperbola without any change in controller gain either above or below eupnoea may promote respiratory stability via increased CO_2 reserve below eupnoea and the reduction in plant gain, despite the increased ventilatory response for any given level of CO_2 above eupnoea [35,43].

It is important to note that significant confusion may arise when considering ventilatory recruitment and CO_2 chemoreflex thresholds, since both terms have been used interchangeably to describe two different inflection points with different neural mechanisms and effects on ventilatory control. The CO_2 chemoreflex threshold is only observed during waking hypocapnic breathing and demarcates the level of CO_2 at which the chemoreflex slope intersects the CO_2-independent wake level of ventilation [38]. A change in this threshold may not reflect any change in the neural mechanisms of chemoreflex control, but rather the neural mechanisms governing minimum wake ventilation associated with the so-called "wake stimulus" (Fig. 1E). Given the slope above and below eupnoea while asleep may not be the same [35], changes in the waking CO_2 chemoreflex threshold may also not impact on chemoreflex control during sleep when the waking stimulus is absent. The neural mechanisms governing the ventilatory recruitment threshold, which demarcates the level of CO_2 required to re-instate rhythmic breathing during hypocapnia in sleep or anaesthesia, are uncertain. However, the ventilatory recruitment threshold can be dissociated from changes to ventilatory drive [25], suggesting a CO_2 "on switch" largely independent of chemoreflex drive (Fig. 1F). Given central apnoea is atypical in OSA the ventilatory recruitment threshold may have little bearing on ventilatory control or LG in OSA pathophysiology.

Cyclical airway collapse via unstable ventilatory control

During wakefulness the upper airway is well protected by excitatory stimuli associated with the wake state, and chemo- and mechano-reflexes that stiffen and dilate the upper airway to prevent airway collapse. At sleep onset wake-related excitatory stimuli are lost and mechanoreceptor reflex responses may be significantly blunted, requiring greater predominance of chemoreflex control of ventilation during sleep. In anaesthetised cats hypocapnia preferentially reduces hypoglossal more than phrenic neural drive [46]. During hypocapnia in anaesthetised rabbits, genioglossal muscle activity ceases before diaphragm activity, and during recovery from hypocapnia phasic activity returns to the genioglossus after the diaphragm. During hypercapnia however, increases in activity above baseline are higher in the genioglossus than in the diaphragm [47]. This differential gain in upper airway versus inspiratory pump muscle drive could promote airway collapse in OSA, firstly by preferentially stimulating upper airway dilator muscles and facilitating hyperventilation post obstruction, and secondly by preferentially inhibiting drive to upper airway dilator muscles during the ensuing hypocapnia. High LG and unstable ventilatory control likely further exacerbate obstruction propensity by increasing the magnitude of change in ventilatory drive between the hyperventilation and subsequent hypoventilation phases.

Several lines of evidence support that hypocapnic airway hypotonia and high LG are both important pathogenic features in OSA. Patients treated for OSA with tracheotomy often continue to exhibit unstable breathing when the airway is totally bypassed [48,49], as do around 15% of OSA patients effectively treated with CPAP [50]. Experimental stomal occlusion in tracheotomised OSA patients results in upper airway obstruction, arousal and sufficient hyperventilation to induce subsequent hypopnoeas and breathing pauses depending on the severity of hypocapnia [51]. Furthermore, breathing pauses were prevented with added inspired hypercapnic hyperoxic gas [51], blunting peripheral chemoreflexes and preventing hypocapnic ventilatory depression. Electromyographic recordings in OSA patients also show that upper airway dilator muscles such as the genioglossus and alae nasi exhibit periodic reductions in drive, with nadir muscle activity coinciding with airway obstruction [52,53]. Similarly, imaging of the airway during

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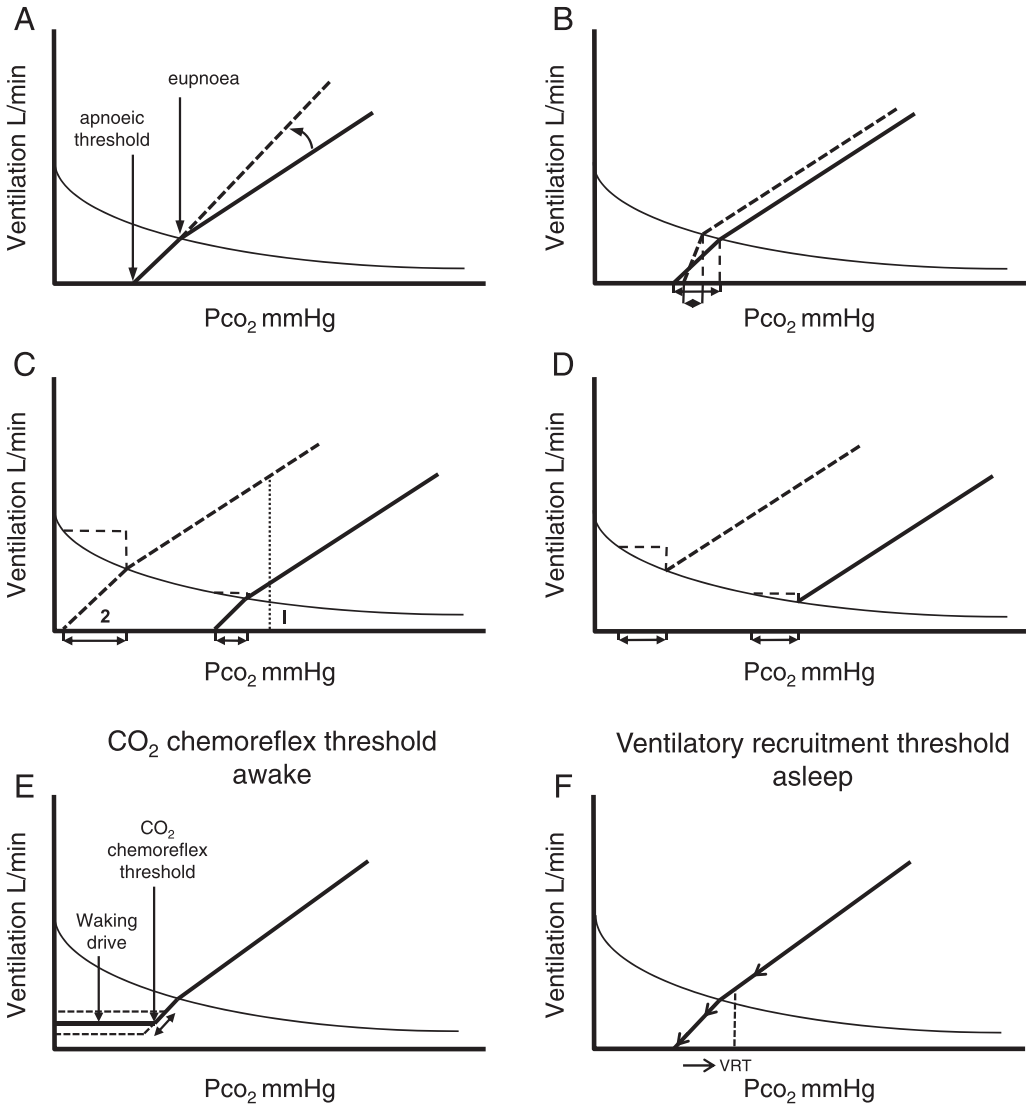

Fig. 1. Potential mechanisms via which changes to sleep chemoreflex control could increase loop gain. A. Increased sensitivity/controller gain to either hypercapnia (above eupnoea) or combined hypercapnic hypoxia. B. A change in either eupnoea or apnoeic threshold to reduce CO_2 reserve and increase controller gain below eupnoea. C. A leftward shift along the metabolic hyperbola with no change in controller gain either above or below eupnoea; 1, increases the magnitude of ventilatory response to hypercapnia and 2, increases the CO_2 reserve below eupnoea. D. A leftward shift along the metabolic hyperbola also decreases plant gain; greater ventilatory overshoot is then required to achieve the same reduction in $PaCO_2$. E. Changes to the waking CO_2 chemoreflex threshold may be due to neural mechanisms governing waking stimulation of ventilation, not chemoreflex control. F. The ventilatory recruitment threshold (VRT) may be independent of chemoreflex drive, merely representing the CO_2 at which ventilation is reinstated after hypocapnic apnoea during sleep.

obstructive apnoeas shows the airway is enlarged during inspiration and passively collapses during end expiration [54]. Even in healthy participants not normally susceptible to sleep disordered breathing, mechanical hyperventilation to produce hypocapnia during sleep induces periodic breathing and both central and obstructive apnoeas [55,56], with pharyngeal narrowing occurring during the expiratory phase [56]. Hypoxia also induces periodic breathing in healthy non-OSA participants due to hyperventilation induced hypocapnia, and peak upper airway resistance and obstruction occurs at the nadir of ventilatory drive [57].

High controller and loop gain in OSA – inherent or acquired?

The contribution of LG as an underlying cause of OSA in any individual patient likely depends on several factors and interactions with other mechanisms in OSA [8,9]. An intrinsically high LG could be an important causal factor in some patients. However, an acquired elevation through obesity and plant gain effects, and/or through neuroplastic changes in controller gain would also be expected to exacerbate OSA in patients with pre-existing OSA.

Using pseudorandom binary stimulation with 4% CO_2 to assess chemo-reflex control, Hudgel and colleagues found less stable breathing control in OSA patients compared to healthy weight non-OSA controls [58]. This did not appear to be due to higher controller gain, implying higher plant gain, perhaps consistent with reduced lung volume in obese OSA patients versus non-obese controls [58]. Plant gain and lung volume were not directly measured and it remains unclear if plant gain differs between OSA patients and non-OSA controls independent of weight. Nevertheless, obesity-related increases in plant gain, and intrinsically high controller gain both appear likely to contribute to OSA in at least some patients.

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More recently with the use of proportional assist ventilation LG has been shown to correlate with the severity of OSA [59]. When patients with a high LG were given supplemental oxygen to suppress peripheral chemoreceptor activity, both apnoea hypopnoea index (AHI) and LG decreased, with no significant effect in patients with a low LG [60]. These findings strongly support that elevated LG through chemoreflex hypersensitivity plays an important causal role in many patients.

Chemoreflex responses in OSA are affected by a range of factors such as age [61], gender [62], weight [63] and comorbidities such as diabetes [64], hypertension [65] and cardiovascular disease [66]. However, when all of these factors were controlled Narkiewicz et al. found that sympathetic nerve activity was higher at baseline in awake OSA patients compared to well matched non-OSA controls. During hypoxia, OSA patients also exhibited a significantly greater increase in minute ventilation, heart rate and mean arterial pressure, indicating greater peripheral chemoreceptor sensitivity in OSA, but with no significant differences between groups in responses to hypercapnia [12]. Other well controlled [67] and large cohort [68] studies have also found no significant differences in waking hypercapnic ventilatory responses (HCVR) between OSA patients and non-OSA controls. However, obesity, a major risk factor in OSA, is an independent predictor of increased central (CO_2) waking chemoreflex sensitivity [63]. The mechanisms responsible for this are not certain, however the authors speculated that it may be due to leptin, as leptin is raised in obesity and mice deficient in leptin show severe blunting of the HCVR [69]. Although OSA does not appear to independently increase CO_2 chemoreflex sensitivity, obese OSA patients may nevertheless exhibit an increased sensitivity to both hypercapnia and hypoxia. Consistent with this, OSA patients have been shown to exhibit an increased dynamic ventilatory response to hypercapnic hypoxia during sleep [14]. During sleep, OSA patients also exhibit a lower eupnoeic $P_{ET}CO_2$ but similar apnoeic threshold compared to healthy age, sex and body mass index matched non-OSA controls [13]. These combined changes in OSA increase controller gain both above and below eupnoea during sleep, and reduce the CO_2 reserve between eupnoea and the apnoeic threshold.

Importantly, chemoreflex control abnormalities in OSA patients have been shown to normalise with the use of CPAP [13,15,16]. Spicuzza et al. found that one month of nasal CPAP significantly decreased the waking ventilatory response to normocapnic hypoxia in moderate to severe OSA from 1.08 ± 0.07 L/min/%SaO_2 prior to treatment to 0.53 ± 0.02 L/min/%SaO_2 after treatment. However, there was no effect on the normoxic hypercapnic ventilatory response [16], a finding similar to that of Foster et al. who also found one month of CPAP had no effect on the HCVR [67]. Given that OSA is not associated with an abnormal HCVR above eupnoea [12,67,68], the lack of CPAP treatment effects on HCVR is not surprising. However, treatment effects below eupnoea and with hypercapnic hypoxia, a more relevant stimulus in OSA, have been demonstrated. Salloum et al. found one month of CPAP significantly increased the gap between eupnoea and the apnoeic threshold from 1.9 ± 0.8 mmHg to 3.7 ± 0.7 mmHg, significantly reducing controller gain below eupnoea during sleep [13]. Loewen et al. found that ≥5 mo of CPAP significantly reduced the dynamic ventilatory response to combined hypercapnic hypoxia during sleep from 131% ± 95%–52% ± 34% of baseline ventilation [15]. Additionally, OSA patients exhibiting treatment emergent central sleep apnoea often show resolution within a few months of treatment, further supporting gradual treatment reversal of underlying unstable breathing control induced by OSA [48,70]. In combination, these findings support that chemoreflex control abnormalities underlying increased controller gain and LG in OSA are predominantly not inherent, but rather induced by OSA itself and are reversible with normal treatment. Thus, elevated controller gain and overall LG appears likely to be *both* a cause of OSA in some patients, and a consequence of OSA that further exacerbates the disorder in a larger group of patients [45,71,72].

Neuroplasticity induced by OSA

Several physiological stimuli associated with OSA have been shown to induce neuroplasticity at different locations in the ventilatory neural network. The most thoroughly studied forms of ventilatory neuroplasticity are those induced by IH. While many different IH protocols have been used [73], the pattern of IH most relevant to OSA is that of short periods (<5 min) of moderate hypoxia (desaturation 70–90%) with sufficient time between repeated hypoxic episodes to achieve normal arterial re-oxygenation (1–5 min in humans). Studies fitting these criteria have used two main designs; acute intermittent hypoxia (AIH) with the number of episodes ranging from three to repeated application across an entire day, and chronic intermittent hypoxia (CIH), typically ranging from three days to several weeks with 8–10 h of exposure per day to simulate recurring IH during sleep. The type of exposure (acute vs chronic) influences the type and location of neuroplasticity induced by IH.

AIH can induce LTF in ventilatory motor neurons, characterised by a sustained increase in whole nerve recording burst amplitude upon returning to normoxia, which may persist for several hours following hypoxic exposure [74]. LTF is only induced following IH and not by the same cumulative duration of sustained hypoxia [75], or by intermittent hypercapnia [76]. LTF following AIH in rats has been reported in the phrenic [77], hypoglossal [78], glossopharyngeal [79] and laryngeal nerves [80]. Phrenic LTF (pLTF) is the most studied form of LTF and manifests as increased V_I, predominantly due to increased tidal volume (V_T), although increased breathing frequency is also sometimes reported [81]. The key stimulus inducing pLTF with IH appears to be peripheral chemoreceptor activation which stimulates serotonergic or adrenergic release from medullary raphe or locus coeruleus neurons [82], respectively, onto relevant respiratory motor neuron pools. In rats, there are two known G-protein coupled intracellular pathways which can be independently activated by AIH to induce pLTF, which are indistinguishable at the phenotypic level (either neural activity or ventilation). These pathways are called the Q and S pathways due to activation of either G_q or G_s protein coupled metabotropic receptors. The pathway activated depends on the severity of hypoxia experienced during IH, with the Q pathway activated by PaO_2 levels above 35 mmHg while PaO_2 levels 30 mmHg or below elicit the S pathway, with cross talk inhibition between the pathways appearing to confer dominance of one pathway at a time [83].

Devinney *et al.* 2013 [85] provide a detailed review of the intracellular mechanisms thought to underpin pLTF. In brief, episodic activation of the serotonin receptor 5-HT_2 or α1-adrenergic receptors elicits pLTF via activation of G_q coupled receptors [84]. The S pathway is activated by episodic activation of the serotonin receptor 5-HT_7 and adenosine 2_A receptors coupled to G_S receptors [86,87]. The two G receptors activate different intracellular pathways, however a key interaction appears to involve the regulation of NADPH oxidase activity and reactive oxygen species (ROS) formation [85]. The Q pathway is dependent on upregulation of NADPH oxidase, which in turn increases synthesis of ROS [74]. ROS regulate the balance of kinase and phosphatase activities and ROS formation during hypoxia/re-oxygenation in IH is thought to confer pattern sensitivity to pLTF by increasing kinase activation and phosphorylation of key proteins required for induction of pLTF [88]. During severe hypoxia the S pathway dominates due to constraint of the Q pathway via activation of protein

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kinase A, which is thought to inhibit NADPH oxidase activity and reduce ROS formation [87]. The ultimate cellular changes resulting in pLTF via the Q and S pathway are still not certain, but glutamate receptor phosphorylation and/or an increase in glutamate receptor insertion into the motor neuron membrane may facilitate post-synaptic neurotransmitter uptake thereby conferring increased neural activity characteristic of pLTF [84]. Of particular note is that the Mitchell laboratory describe phrenic motor facilitation as a general term for enhanced phrenic motor output, whereas pLTF selectively refers to the form induced by AIH which activates the serotonergic Q pathway [84]. For simplicity, we refer to all AIH induced phrenic motor facilitation as pLTF.

Hypoglossal LTF (hLTF) increases phasic genioglossal electromyographic activity, but has also been reported to facilitate both protrudor and retractor upper airway muscle activity in adult male rats [78]. Much less is known about hLTF than pLTF, although hLTF appears to share similar mechanisms to pLTF, with both dependent on episodic serotonin stimulation [77] and formation of ROS [89]. However in rats, pLTF is more consistently induced with IH, while hLTF is not induced in certain rat strains and is inhibited by low testosterone levels and vagal feedback [90].

Three or more days of IH (i.e., CIH) induces LTF of afferent carotid body activity, or so-called "sensory" LTF (sLTF) characterised by increased basal neural discharge [32], and also increases carotid body hypoxic sensitivity [17]. In rats and mice, CIH induced sLTF has been shown to be mediated by both serotonin and angiotensin II. Episodic application of serotonin to ex-vivo carotid bodies activates 5-HT_2 receptors which activate protein kinase C [91], and episodic angiotensin II application activates angiotensin type 1 receptors [92], both of which activate NADPH oxidase-2, increase ROS production and induce sLTF [92,93]. In adult male rats CIH has been shown to increase carotid body hypoxic sensitivity via an independent pathway to sLTF involving ROS mediated activation of endothelin converting enzyme, which then upregulates endothelin 1 leading to activation of endothelin A receptors [94]. As with AIH induced motor facilitation, the ultimate mechanisms leading to sLTF and increased carotid body hypoxic sensitivity following CIH are also uncertain, but appear to be via independent mechanisms associated with ROS dependant recruitment of serotonin and endothelin-1, respectively [95]. Both sLTF and increased carotid body hypoxic sensitivity in rats are reversible within ten days of returning to room air breathing [17,32]. Kumar et al. 2012 [96] provide a more comprehensive review of CIH induced carotid body neuroplasticity.

IH also induces changes at multiple sites within the brainstem involved in both the induction and maintenance of LTF and transduction of chemoafferent activity. Changes in firing rate and connectivity between raphe neurons, nucleus tractus solitarus and the ventral respiratory group neurons have been recorded in decerebrate and vagotomised cats following acute episodic carotid chemoreceptor stimulation and induction of pLTF [18]. AIH in rats induces increased sympathetic nerve activity and pLTF, both of which were blocked by systemic pre-treatment with methysergide, a serotonin receptor antagonist [97]. This suggests neuroplasticity within brainstem serotonergic pathways involved in sympathorespiratory coupling may underlie the increased sympathetic neural activity seen in OSA [12,97]. Carotid body sLTF following CIH would be expected to further augment sympathetic neural activity, which is thought to contribute to hypertension and cardiovascular disease in OSA [98]. CIH in rats increases aminergic terminals and receptors in the hypoglossal and trigeminal (which innervates palatal muscles and contributes to airway patency) motor nuclei [99,100]. As aminergic excitatory drive to the hypoglossal motor neuron pool is state-dependant, being highest in wake and lowest in REM sleep [101], CIH induced increases in aminergic terminals and receptors may contribute to the adaptive wake related increase in upper airway dilator muscle activity seen in OSA [100,102].

In addition to IH, other stimuli experienced during repetitive obstructive apnoeas, such as episodic vagal feedback [103], negative upper airway pressure [104] and withdrawal of motor neuron activity [105], have been shown to induce LTF in various motor neurons and respiratory muscles in rats. Whether these forms of neuroplasticity also occur in humans has yet to be determined, so their relevance to OSA is uncertain.

Neuroplasticity in humans versus animal models

LTF appears to be particularly difficult to elicit in awake vagally intact preparations, and even under highly controlled experimental conditions in IH studies using anaesthetised animals, 10% of preparations fail to exhibit LTF [106]. This may be partly due to the differential effects of vagal feedback on hLTF versus pLTF [107]. Arousal states may also be important given that LTF is difficult to induce during wakefulness, but progressively more readily induced in deepening NREM sleep in Lewis rats [108]. This could reflect that raphe neurons fire at or near maximal activity during wakefulness and show reduced activity with decreasing arousal state, providing a greater dynamic range of firing potential during deep sleep [28]. Sex, age and genetic variation are also known to influence whether LTF is induced in animals [20], although similar sex differences in the manifestation of ventilatory LTF ($_V$LTF) or sensitisation of the HVR have not been noted in humans [109,110]. Given many potentially important uncontrolled variables it is perhaps not surprising that many IH studies conducted in awake healthy humans have failed to elicit LTF [30,111–114]. Studies in sleeping humans have also reported mixed results. Some report reduced upper airway resistance in OSA patients but no increase in ventilation [115,116], another reports increased genioglossal activity in non-OSA participants without increased ventilation [117], while another reports increased ventilation among snorers [118]. Variable results in humans may also be due to differences in hypoxia protocols, wake influences on ventilation and, perhaps most importantly, the level of concomitant CO_2 used during IH.

Olson and colleagues found that in unanaesthetised, unrestrained rats maintained in a poikilocapnic environment, increased ventilation following LTF induction lead to hypocapnia and subsequent central depression of LTF expression. When CO_2 was supplemented back to baseline levels, LTF was equivalent in magnitude to previous findings of phrenic LTF in anaesthetised, vagotomised and paralysed preparations [119]. These data suggest that CO_2 levels are a critical determinant of LTF expression. Mateika and colleagues have proposed that since waking stimuli maintain ventilatory rhythmicity even below the arterial CO_2 required for chemostimulation [37], and as most earlier studies in humans had not determined the CO_2 chemoreceptor threshold prior to experimentation, low CO_2 during and after IH may have suppressed LTF expression [30]. The same group demonstrated that LTF of ventilation and peak genioglossus muscle activity could be elicited in awake healthy humans in the presence of sustained mild hypercapnia (5 mmHg above normocapnia), but that when normocapnia was reinstated LTF became masked with V_I constrained to normocapnic baseline values [21]. Given that hypoxia elicits cerebral vasodilation, Pierchala and colleagues theorised that prolonged hypoxia utilised in many human studies may result in cerebral hypocapnia and central ventilatory depression which may reduce the stimuli required to induce LTF. With the use of shorter isocapnic hypoxic exposures (<1 min) during sleep in healthy humans, the same authors demonstrated $_V$LTF and upper airway LTF ($_{UA}$LTF) via increased V_I and V_T and decreased upper airway resistance [120].

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Consequently, CO_2 levels and feedback appear to critically influence both the induction and expression of LTF.

Similar to animal studies, Mateika, Badr and colleagues have shown that LTF and increased HVR can be induced in humans, but with some notable differences. AIH in humans has been shown to induce both $_{V}$LTF and $_{UA}$LTF [21,120,121] (thought due to pLTF and likely other pump muscle motor neurons, and hLTF, respectively) and to induce progressive augmentation (PA) of the HVR with each successive hypoxic episode [21,121]. In humans, similar to animal studies, CO_2 feedback constrains $_{V}$LTF in the presence of poikilocapnia [21,119] and AIH reduces eupnoeic $P_{ET}CO_2$ [29,30]. However, AIH also reduces the apnoeic threshold in rats [25], but not in humans [29]. Consequently in humans, AIH reduces the CO_2 reserve between eupnoea and apnoea thereby increasing controller gain below eupnoea [29].

CIH in animals increases carotid body hypoxic sensitivity [17] and the magnitude of pLTF induced by AIH [122], and greater $_{V}$LTF and HVR with AIH in OSA patients compared to matched non-OSA participants is consistent with similar CIH effects in OSA [121]. As with CIH in animals [122], these effects in humans appear to depend on ROS formation since the degree of oxidative stress during CIH correlates with HVR changes [31], and administration of antioxidants prior to IH diminishes LTF and HVR responses in OSA patients [121]. CIH induced $_{V}$LTF and increased HVR in humans is also reversible within four days after returning to room air breathing [31,33], similar to the reversible nature of $_{V}$LTF, sLTF and increased carotid body hypoxic sensitivity in rats upon return to room air breathing [17,32,123]. Following 30 brief hypoxic voluntary apnoeas, awake humans exhibit increased muscle sympathetic nerve activity, blood pressure and acute HVR [124]. Similarly, AIH in rats induces serotonin dependent increased sympathetic nerve activity [97], while CIH in rats also induces hypertension [125].

In rats and cats increased carotid body hypoxic sensitivity only occurs after a minimum of three days CIH [17,126], while humans consistently show progressive augmentation of the HVR during AIH [21,121] and during CIH after the first day of exposure [31]. Whether these findings reflect species differences in carotid body neuroplasticity are uncertain. It is possible that the increased HVR seen in humans following AIH may be due to pLTF and $_{V}$LTF raising basal ventilation, resulting in an increase in peak HVR. Alternatively, neuroplasticity within brainstem regions facilitating central integration of chemoafferent activity could increase the HVR [18,97,123], without any change in carotid body chemosensitivity (Refer to [40] for detailed discussion of variables affecting HVR measurements). The mechanisms of AIH induced increased HVR in humans and the contribution of central versus carotid body neuroplasticity warrants further investigation.

Does IH and LTF help stabilise the airway?

Given that hLTF increases upper airway muscle activity it has been suggested that hLTF could help to stabilise the airway and protect against OSA [27]. However, since OSA persists without treatment and returns with treatment withdrawal, hLTF protective effects may be relatively modest. Mateika and Narwani have proposed that hLTF may be maladaptive and exacerbate OSA by further dilating the airways upon airway re-opening, increasing the magnitude of hyperventilation and hypocapnia, subsequently exaggerating the decrease in ventilatory and upper airway muscle activity and propensity for airway re-collapse [28]. Rowley and colleagues partly tested this concept by examining upper airway resistance and the pressure at which the airway collapses during sleep in OSA patients before and after AIH exposure on CPAP. The authors found no evidence of $_{V}$LTF or altered airway collapsibility, although upper airway resistance was significantly decreased suggestive of $_{UA}$LTF. As there was no change in airway collapsibility the authors concluded that $_{UA}$LTF does not help to stabilise the airway in OSA patients [116].

A recent study of chronic effects of IH in OSA patients found that ten days of CIH induced $_{V}$LTF and sensitised the HVR, and these changes were clearly not protective as OSA severity increased [127]. HVR changes correlated with increases in AHI, mixed apnoea frequency and apnoea duration and were also accompanied by greater oesophageal pressure and V_T after apnoea termination, indicating greater hyperventilation and more unstable ventilatory control following daytime CIH exposure [127]. $_{V}$LTF induced by daytime CIH did not correlate with any sleep ventilatory parameter, or help to stabilise breathing in sleep. The same laboratory also reported that AIH presented during sleep in male and female OSA patients on therapeutic CPAP induced $_{V}$LTF and increased AHI without increasing the HVR [109,110]. Increased AHI with increased HVR induced by experimental CIH [127] is consistent with CIH effects in untreated OSA where higher LG correlates with increased AHI [59], and hyperoxic suppression of carotid body activity reduces both LG and AHI [60]. In combination, these findings support that both $_{V}$LTF and increased HVR induced by IH contribute to increasing LG, respiratory instability and AHI.

An important reason why hLTF may not stabilise the airway in OSA could be that to do so would require hLTF expression independent of chemoreceptor drive for augmented muscle activity to be maintained during the post obstruction hypocapnic hypoventilation phase. Hypocapnic suppression of LTF has been demonstrated in both humans and rats [21,119], and most likely reflects post synaptic changes underpinning LTF at the motor neuron level. Given motor neuron LTF is thought to be due to facilitation of post-synaptic excitatory neurotransmission [20], reduced excitatory stimuli during hypocapnia would render LTF incapable of amplifying motor neuron output. Nevertheless, although suppressed during hypocapnia, robust pLTF has been demonstrated once normocapnia or hypercapnia are re-instated [36]. Consequently, hLTF would be expected to be inhibited during hypocapnic hypoventilation, and to be preferentially expressed during normocapnia and hypercapnia; thereby facilitating hyperventilation by further dilating the airways, potentially exacerbating post-obstruction hypocapnia. For this reason hLTF could promote cyclical obstruction, even without changes in chemoreflex control or $_{V}$LTF.

IH increases LG

Despite a large body of work examining IH and LTF effects relevant to respiratory muscle control and OSA pathophysiology, currently there is only indirect evidence to support that LTF is expressed in OSA. A comparison of resting ventilatory parameters between normotensive and hypertensive OSA patients and non-OSA controls found that hypertensive OSA patients had a higher resting V_T, suggesting higher tonic resting chemoreceptor drive than in normotensive OSA patients and controls [128]. Modified rebreathing tests in OSA patients compared to age, race, sex and weight matched controls found that OSA patients have a higher resting V_I due to a higher V_T [129]. OSA patients also exhibit a lower eupnoeic $P_{ET}CO_2$ [13] consistent with vLTF producing a leftward shift in eupnoea along the metabolic hyperbola via CO_2 feedback.

Perhaps the strongest evidence that repetitive IH in OSA has long-lasting neuroplastic effects which increase LG comes from studies showing that abnormal chemoreflex responses induced by experimental IH are also present in OSA patients and are reversed by CPAP treatment (Fig. 2). This suggests induced rather than inherent chemoreflex control disturbances. These disturbances include increased HVR [12,16], reduced eupnoeic $P_{ET}CO_2$ [13] and an increased ventilatory response to combined hypercapnic hypoxia [14,15,30]. These changes combine to reduce the CO_2 reserve

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between eupnoea and the apnoeic threshold, and increase controller gain both below and above eupnoea during hypercapnic hypoxia. Although the leftward shift along the metabolic hyperbola would decrease plant gain, this effect is likely to be small with the net effect remaining increased controller gain and overall LG. As a consequence, the magnitude of post-obstruction hyperventilation would be expected to increase, exacerbating post-obstruction hypocapnia and upper airway hypotonia, potentially promoting airway collapse and increasing OSA severity. This is further supported by findings of increased AHI following CIH in OSA [127], and reduced AHI and apnoea duration following 30 days of antioxidant treatment alone without CPAP, suggesting that ROS with IH contributes to cyclical airway obstruction in OSA [130].

It is possible that under certain conditions neuroplastic changes which increase controller and LG ($_V$LTF and increased HVR) may be depressed while hLTF remains expressed. For example, despite airway deficits OSA patients frequently exhibit prolonged periods of stable breathing in sleep with increased genioglossal muscle activity, particularly during slow wave sleep [131,132]. This could at least partly reflect blunted chemoreflexes and lower controller gain above eupnoea during slow wave sleep [133,134]. As chemoreflex drive drops, V_I decreases [135] and $PaCO_2$ increases with a rightward shift along the metabolic hyperbola (Fig. 3). If the apnoeic threshold remains unchanged this would widen the CO_2 reserve and decrease controller gain below eupnoea. Although there would be a small concomitant increase in plant gain (i.e., a smaller ventilatory overshoot would cause a greater reduction in $PaCO_2$) this is unlikely to fully counteract reduced controller gain both above and below eupnoea. Consequently, overall LG would be expected to decrease during slow wave sleep leading to reduced hyperventilation and hypoventilation and more stable CO_2. More stable and elevated CO_2 would likely also facilitate ongoing expression of hLTF. When combined with an increased arousal threshold (more difficult to wake) in slow wave sleep [136], hLTF could more effectively augment upper airway muscle activity towards sustaining stable breathing without arousal. Thus, a combination of interacting factors may underpin markedly improved OSA severity in slow wave sleep.

Clinical significance

Treatments to reduce LG have significant future potential given frequent CPAP non-adherence [7] and emerging methods to quantify variable and interacting deficits underpinning OSA [9]. Oxygen therapy and pharmacological agents such as acetazolamide show significant promise [10,60], although potential side effects may make long term treatment unsuitable. Elevated plant gain

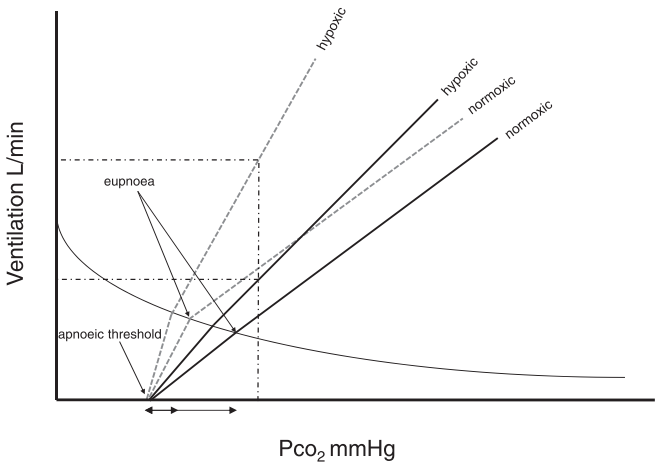

Fig. 2. Schema of potential changes induced by IH in OSA and effects on ventilatory control during sleep. Black lines represent ventilatory response to CO_2 during sleep under normoxic and hypoxic conditions in healthy normal controls. Grey dashed lines represent chemoreflex control changes induced by experimental intermittent hypoxia (IH). Equivalent chemoreflex control changes are seen in obstructive sleep apnoea (OSA) patients, and normalise following continuous positive airway pressure treatment. Under normal conditions, prior to IH, ventilation changes linearly with changing CO_2 above and below eupnoea down to the apnoeic threshold where ventilatory drive ceases. Hypoxia increases the sensitivity to CO_2 and causes eupnoea to shift leftward along the metabolic hyperbola, reducing the CO_2 reserve and increasing controller gain below eupnoea. IH induced ventilatory long term facilitation ($_V$LTF) increases minute ventilation but this effect is constrained by CO_2 feedback causing a leftward shift along the metabolic hyperbola during poikilocapnic normoxia. Although IH does not increase sensitivity (controller gain) to CO_2 above eupnoea, $_V$LTF reduces the CO_2 reserve and increases controller gain below eupnoea under normoxia. Chronic IH sensitises the ventilatory response to hypoxia, increasing controller gain above eupnoea under hypercapnic hypoxic conditions. Due to CO_2 feedback, under hypoxic conditions after IH the point of eupnoea would shift further left along the metabolic hyperbola, further decreasing the CO_2 reserve below eupnoea and further increasing controller gain below eupnoea. Dotted lines represent ventilatory response to combined hypercapnic hypoxia (hypothetical chemoreflex drive at airway re-opening) before versus after IH induced changes in chemoreflex control. These changes would be expected to increase controller and overall loop gain to cause a greater degree of post-obstruction hyperventilation, hypocapnia and upper airway hypotonia, thereby promoting airway re-obstruction and increased apnoea hypopnoea index (Data compiled from [12–16,21,29,30,119–121]).

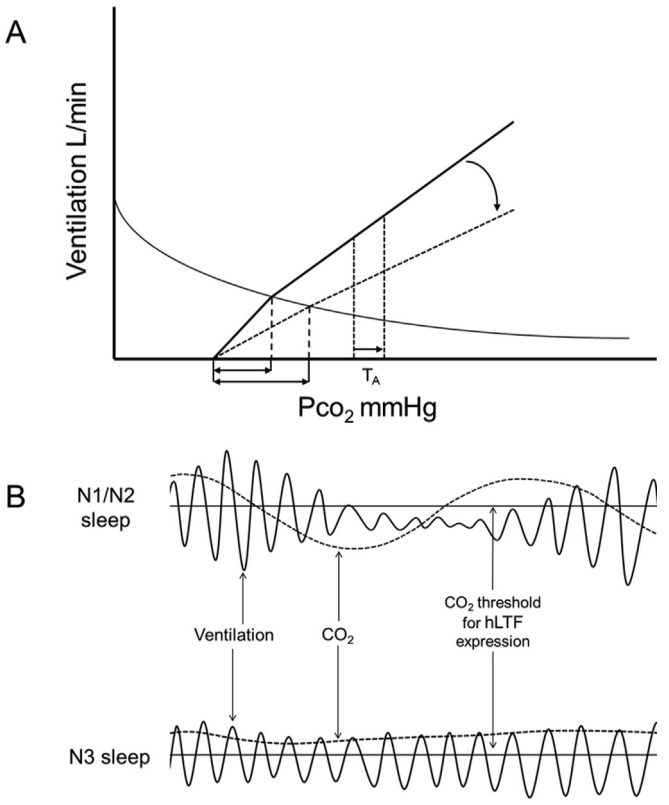

Fig. 3. Possible effects of slow wave sleep on LG and hLTF expression. A. During slow wave sleep chemoreflex sensitivity above eupnoea decreases, reducing minute ventilation and increasing end-tidal CO_2 ($P_{ET}CO_2$), resulting in a rightward shift of eupnoea along the metabolic hyperbola. This would widen the CO_2 reserve and reduce controller gain below eupnoea. Reduced controller gain above and below eupnoea would reduce overall loop gain (LG). In addition, an elevated arousal threshold (T_A i.e., more difficult to awaken) in slow wave sleep allows for greater tolerance of augmented ventilatory drive without arousal. B. Reduced LG would stabilise ventilation and $P_{ET}CO_2$. Higher and more stable CO_2 would facilitate continual expression of hypoglossal long term facilitation (hLTF). In conjunction with increased T_A, hLTF would also facilitate increased upper airway muscle activity without arousal, thus allowing more stable breathing in slow wave sleep.

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from reduced lung volume in obesity may be difficult to correct without weight loss. However, controller gain abnormalities induced by IH could be more important in many patients. Given these appear to normalise with treatment [13,16], long term pharmacological manipulation of LG may not be necessary, and other traits could potentially be treated with suitably targeted combination therapies following normalisation of LG. Reduced LG post-treatment might also influence CPAP requirements and warrant re-titration, potentially improving long-term CPAP tolerance and adherence.

The neuroplastic changes to chemoreflex control which increase controller gain and therefore LG are dependent on ROS production [89,93,137]. Pre-treatment with antioxidants in both rats and humans can block IH induced neuroplasticity [121,122,138]. In addition, antioxidant administration without CPAP has been shown to reduce AHI and apnoea duration [130]. Furthermore, ROS are thought to play a causal role in many of the OSA associated pathologies such as cardiovascular disease [2], neurologic pathologies [4,139] and diabetes [140]. Antioxidant treatment alone may be sub-optimal, but in patients not able to tolerate CPAP or other treatments, could nevertheless help to stabilise breathing, reduce OSA severity and ameliorate other ROS mediated comorbidities.

Summary and future research directions

Unstable ventilatory control with high LG is now recognised to be one of the key non-anatomical factors underpinning cyclical airway obstruction in OSA [8], predominantly via increasing the magnitude of post-obstruction hyperventilation promoting hypocapnic upper airway muscle hypotonia and recurring obstruction. OSA patients exhibit an elevated HVR [12] and a reduced eupnoeic $P_{ET}CO_2$ [13] which combine to increase controller gain and overall LG. These abnormalities are reversed with CPAP treatment [13,16], indicating they are an induced consequence of OSA rather than a primary underlying causal trait. Hence, LG is both an inherent and induced trait, and both a cause and a consequence of OSA [45,71,72]. Although it has been suggested that IH induced $_{V}$LTF and hLTF could potentially help protect against OSA [27,141], several human studies do not support this, and have instead shown an increase in AHI and thus an exacerbation of OSA [109,116,127]. Due to ventilatory feedback in a poikilocapnic environment, $_{V}$LTF reduces eupnoeic $P_{ET}CO_2$ [119] and CO_2 reserve [21,29], thereby increasing controller gain below eupnoea. In conjunction with IH induced sensitisation of the HVR [21], controller gain above eupnoea during hypercapnic hypoxia also increases [30]. This combination of IH induced $_{V}$LTF and increased HVR is likely the mechanism causing elevated controller gain and LG in OSA. Motor neuron LTF is dependent on chemoreflex drive and is inhibited by hypocapnia [36]. Consequently, hLTF is most likely incapable of facilitating upper airway dilator muscle activity during the post-obstruction hypocapnic hypoventilation period, and possibly exacerbates hyperventilation during the hypercapnic hyperventilation phase by facilitating airway dilation.

CPAP treatment in OSA patients reduces the HVR and normalises eupnoeic $P_{ET}CO_2$, thereby reducing controller gain both above and below eupnoea [13,16]. Similarly, IH induced sLTF and increased carotid body hypoxic sensitivity in rats [17,122], and $_{V}$LTF and increased HVR in humans is reversible within several days of returning to room air breathing [31,33]. Collectively, these findings support that conventional CPAP treatment allows reversal of ventilatory neuroplasticity underpinning elevated LG. However, there remains an ongoing debate regarding the contribution of induced controller gain abnormalities versus inherent LG traits in OSA [45,72]. Further work in this area appears to be warranted given elevated LG in many OSA patients [9], CPAP reversal effects, non-CPAP treatment approaches to lower LG [10], and ongoing uncertainty regarding the contribution of inherent plant and controller gain versus induced controller gain abnormalities in OSA.

Airway obstruction induces concomitant hypercapnic hypoxia rather than IH alone and yet there are very few human or animal studies of the effects of intermittent hypercapnic hypoxia on ventilatory neuroplasticity. The chosen level of isocapnia during and following IH significantly impacts both the induction and expression of LTF [21]. Intermittent hypercapnia alone also induces a form of noradrenergic dependent respiratory depression rather than serotonergic LTF [76,77]. Consequently the effects of intermittent hypercapnic hypoxia may well differ from those of IH. Further studies of intermittent hypercapnic hypoxia and the role of CO_2 in IH induced neuroplasticity are needed to better understand OSA pathophysiology.

Due to the significant role that ROS play in neuroplasticity of ventilatory control [74,88,92] and comorbidities associated with OSA [2,140], and evidence that antioxidants can both block IH induced neuroplasticity [121,122,138] and reduce AHI in untreated OSA patients [130], future research investigating potential therapeutic benefits of antioxidant treatment in OSA patients is warranted.

Practice points

Intermittent hypoxia induced neuroplasticity increases loop gain and likely exacerbates OSA. This is supported by:

1) An increased hypoxic ventilatory response and reduced eupnoeic $P_{ET}CO_2$ and CO_2 reserve below eupnoea in OSA produce elevated controller gain below and above eupnoea, and increased overall loop gain.
2) These abnormalities are ameliorated with treatment, indicating induced rather than inherent high controller gain.
3) Intermittent hypoxia induces the same changes in chemoreflex control via increased carotid body hypoxic sensitivity and ventilatory motor neuron long term facilitation. Via CO_2 feedback, ventilatory long term facilitation reduces eupnoeic $P_{ET}CO_2$ and CO_2 reserve.
4) IH induced neuroplasticity reverses within days upon return to room air breathing.
5) Treatments which prevent OSA and IH, such as CPAP, may reduce LG.

Research agenda

To better understand pathophysiological effects of intermittent hypoxia induced neuroplasticity in OSA future research should focus on determining:

1) Effects of intermittent hypoxia on loop gain.
2) Continuous positive airway pressure treatment effects on loop gain.
3) Whether hypoglossal long term facilitation is protective or promotes cyclical obstruction in OSA.
4) Whether neuroplastic effects of combined intermittent hypercapnia and hypoxia reflect those induced by intermittent hypoxia.
5) Potential therapeutic benefits of antioxidants in OSA.

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